Assessment of Exercise Capacity

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1.0. Factors limiting exercise capacity

Exercise intolerance refers to patient's inability to undertake physical task at the level and/or for the duration that would be expected considering his or her age and general functional capacity. When this inability is caused by impaired function of one or more of the physiological body systems (i.e.: central hemodynamic, respiratory, peripheral muscles) the result is the amplification of the sensations of dyspnea and peripheral muscle discomfort that is often initiated by peripheral muscle fatigue [1].

Dyspnea is typically perceived as the distressing sensation of unsatisfied inspiration (i.e.: neuro-mechanical coupling) [2]. The physiological mechanisms that intensify dyspnea sensations occur to the imbalance between the central respiratory efferent drive and the response of the respiratory muscles. In chronic lung disease patients, breathlessness is amplified during exercise consequently to both deteriorating ventilatory mechanics and the increased ventilatory demand.

Peripheral muscle fatigue, associated with the subjective feeling of lower limb discomfort, is demonstrated by a decrease in muscle force output and it is due to a limited oxygen supply to, and/or utilization of oxygen by, the mitochondria [3]. In support of this statement exercise-induced quadriceps muscle fatigue in COPD negatively correlates with peak oxygen uptake [4]. Accordingly, cellular oxygen could either exceed the normal capacity for maximal oxygen transfer of the oxygen transport chain, (i.e.: this is when maximal oxygen uptake has been truly achieved), or stresses an impaired physiological system preventing the achievement of a true maximal oxygen uptake (i.e.: achieving, as in COPD, peak but not true normal maximal oxygen uptake) [5]. In the latter case, a series of failures at the level of respiratory and cardiovascular systems may impair the normal peripheral muscle oxygen delivery and conductance capabilities [3, 6]. Hence, the factors that restrict exercise capacity in healthy

individuals (the former case) are different to that constraining exercise capacity in patients with respiratory diseases (the latter case).

1.1. Exercise testing in lung diseases

To evaluate exercise intolerance, cardiopulmonary exercise testing (CPET) is considered the gold standard as it allows simultaneous assessment of objective (i.e.: cardiopulmonary responses, operational lung volumes, etc.) and subjective variables (intensity of dyspnea and leg discomfort sensations). There are two exercise protocols performed either on the treadmill or the cycle ergometer that are commonly used: the incremental test to the limit of tolerance and the constant-load test.

The incremental test to the limit of tolerance induces a smooth gradational stress of all physiological systems during exercise with progressively increased intensity to volitional termination. The incremental test to the limit of tolerance facilitates both determination of several physiological responses at the point of exercise limitation (i.e.: peak oxygen uptake) and the evaluation of trending phenomena as the severity of exercise advances from sub-maximal to maximal tolerable levels. Such trends may, for example, refer to the increase in minute ventilation relative to oxygen uptake ($\dot{V}O_2$) or to carbon dioxide production ($\dot{V}CO_2$), indicating "ventilatory efficiency". Also, the rate of change in $\dot{V}CO_2$ relative to the change in $\dot{V}O_2$ is commonly used to non-invasively identify the "anaerobic threshold". Similarly, when exercise in undertaken on the bicycle ergometer, the rate of change in $\dot{V}O_2$ relative to work rate is taken to reflect "aerobic work efficiency" (Figure 1) [7].

During constant load exercise the work rate is fixed at a constant fraction of the pre-determined maximal or peak work rate (typically 50-80%) and individuals are required to exercise for as long as they can tolerate the externally imposed workload.

The time to the limit of tolerance is recorded. During these tests, a steady-state response (where the energy demands of the working muscles are met by the energy supply mechanisms) may or may not be achieved depending on the work intensity and the disability level of the individual. Nevertheless, even if a steady-state in the cardio-respiratory response is to be achieved, this will not occur instantaneously but it will happen over a period of time. Hence, the time of dynamic regulation in cardio-respiratory and metabolic physiological responses provides useful information of the dynamic conduct of the respiratory and cardio-respiratory function and of the capacity of the cardiorespiratory and metabolic systems to reach a steady-state of oxygen utilization [1, 5].

Besides the aforementioned incremental and constant load cardiopulmonary exercise tests that provide plethora of information on physiological responses, there are exercise tests that yield less physiological information, but still provide a measure of exercise capacity. The most common ones are the 6-minute walking test [8], and the incremental and endurance shuttle walking tests [9, 10], which provide an indication of exercise intolerance, the intensity of breathlessness and leg dicomfort, and the degree arterial oxygen desaturation. The 6-min walking test is of sub-maximal intensity and is commonly used to determine the effects of various pharmaceutical and non-pharmaceutical interventions on patients' exercise capacity [11, 12]. Patients are allowed to walk at own pace and encouraged to go around a set of cones positioned on the floor as many times as possible. One study [11] indicated that this test yields a highly sustainable oxygen uptake, thereby emphasizing the important prognostic value of the 6-min walking test.

During the incremental shuttle walk test [9] the walking speed is progressively increased until the point where the patient reaches the limits of his/her tolerance.

Accordingly, the incremental shuttle walk test is considered as equivalent to the maximal incremental test performed on the treadmill. The intensity of the endurance shuttle-walk test corresponds to a fraction of the individual patient's maximum exercise performance assessed by the incremental shuttle walk test. Although the sustained intensity is sub-maximal (i.e.: 75 and 85% of intensity) [10] patients commonly reach the limits of their tolerance.

1.2. Factors determining exercise tolerance in healthy young individuals

In healthy subjects exercise tolerance refers to the capacity of an individual to achieve the maximum attainable amount of work during an exercise protocol where the intensity increases progressively until maximum capacity is reached. In this case, exercise tolerance is assessed by the maximum capacity of the individual's body to transport and utilize oxygen (i.e.: $\dot{V}O_2$ max). In turn the achieved $\dot{V}O_2$ max depends on the convective and conductive oxygen delivery and muscle oxygen utilization [3].

Over the past few decades, a number of studies have been conducted with the aim to investigate the limiting factors for achieving $\dot{V}O_{2max}$ in healthy subjects [13-15]. A fundamental approach to establish the limiting factors is to compare the physiological responses recorded from sedentary and well-trained individuals during incremental exercise. Such studies have clearly shown that in healthy sedentary subjects compared to highly-trained athletes the main variable that limits $\dot{V}O_{2max}$ is cardiac output [16-19]. In fact, the implemented experimental procedures demonstrated a linear relationship between $\dot{V}O_{2max}$ and maximal cardiac output showing that an average of 5.0 l/min to 6.0 l/min of cardiac output is needed per liter of $\dot{V}O_2$ in sedentary subjects, whereas in highly-trained subjects cardiac output often reaches 6.0 to 7.0 l/min per liter

of $\dot{V}O_2$. This difference in maximal cardiac output and $\dot{V}O_2$ between sedentary and well-trained subjects was mainly attributed to the lower stroke volume in untrained compared to trained individuals [15]. Additionally, the lower hemoglobin concentration exhibited by the sedentary individuals has been considered as another contributor to the difference in $\dot{V}O_{2max}$ [16-19] as this impacts on the arterial oxygen content. Experimental reduction in maximal cardiac output and in arterial oxygen content (either through the reduction in blood volume or hemoglobin concentration alone) has lead to a reduction in systemic oxygen delivery [20-24].

Besides systemic oxygen delivery, skeletal muscle oxygen extraction as well as mitochondrial rate of oxygen consumption has also been shown to differentiate a sedentary from a well-trained individual in terms of the potential to achieve a high value for $\dot{V}O_{2max.}$ Specifically, skeletal muscle oxygen extraction limitation could be due to: 1) limited diffusive conductance for oxygen between the red blood cells and the mitochondria; 2) non-uniformity of perfusion in relation to metabolic rate; and/or 3) shunting of blood between arterioles and venules, bypassing muscle fibers [1]. The limited diffusive conductance for oxygen appears to be the major contributor in limiting oxygen transport by limiting oxygen extraction [1, 3].

As a final point, $\dot{V}O_2max$ can be affected also by factors as alveolar ventilation/pulmonary perfusion ($\dot{V}_A/Q$) inequality [25] and post pulmonary shunts [26] which are playing a small but demonstrable role in reducing arterial oxygenation [27]. Accordingly, in healthy subjects a limitation primarily in oxygen transport but also in the capacity of oxygen utilization by the working muscles constitutes important factors determining exercise capacity. Defects in the mechanism of oxygen transport and utilization also determine the magnitude of exercise intolerance in patients with chronic lung diseases.

1.3. Factors determining exercise tolerance in healthy-elderly individuals

The response of the cardiovascular and respiratory systems during exercise is attenuated to various degrees in the elderly. Importantly, there are considerable changes in the connective tissue matrix of the lung that may reduce the elastic recoil pressure and hence the airway radial traction, thus predisposing to expiratory flow limitation and air trapping [28]. This justifies common clinical practice to contrast the physiological responses recorded in patients with lung disease with those of healthy age-matched individuals.

The limited capacity of the older adult to increase convective oxygen delivery and muscle oxygen utilization is due to age-related changes in cardiovascular structure and function [29, 30] as well as in mitochondrial content and quality [31]. These factors contribute to a slowed adjustment of muscle oxygen consumption and occurrence of premature metabolic acidosis in the older compared to the young individual [32, 33]. In addition, ageing is accompanied by a reduction in maximal heart rate [34], left ventricular function [30], increased total peripheral resistance [29], diminished capillary density [35], endothelial dysfunction and impaired capillary haemodynamics [36]; all of these limitations are expected to compromise the convective oxygen transport to working muscles during exercise. In addition, during ageing pulmonary vascular stiffness, resistance and pressures are increased along with the heterogeneity of alveolar ventilation and pulmonary perfusion, whilst pulmonary capillary blood volume and membrane diffusing capacity are decreased, thereby causing a reduction in alveolar-capillary surface area [37].

In addition, ageing is associated with several structural and functional changes, related to reductions in the elastic recoil of the lung, in chest wall compliance and in respiratory muscle performance [38-40]. As the compliance of the lung increases and that of the chest wall decreases at a higher degree than that of the lung, thoracic expansion becomes limited; thus an older individual would have to perform ~20% more elastic work at a given level of minute ventilation compared to a 40-year younger fellow [38]. Consequently, the respiratory muscles of the older individual would be expected to work harder given that they are acting on a stiffer chest wall [41-43]. This would increase the share of cardiac output to the respiratory muscle that could potentially limit blood flow to the locomotor muscles [43, 44].

Based on the above, chest wall volume regulation would be expected to differ among old and healthy individuals. Although a similar pattern to that described for healthy young adults [45, 46] has been reported in healthy older subjects, in respect of reducing end-expiratory chest wall volume during progressively increased exercise intensities [47], at peak levels of exercise end-inspiratory chest wall volume in older individuals often reaches ~80% of the chest wall volume at total lung capacity (TLC). In contrast,in healthy young subjects the ratio of end-inspiratory lung volume to TLC does not usually exceed 70% [43, 46]. This disparity exists because young subjects reduce end-expiratory chest wall volume by expiratory muscle recruitment during progressively increased exercise intensities, thus allowing tidal volume to expand by encroachment into both the inspiratory and expiratory reserve volume. In elderly, consequently to flow limitation at advanced levels of exercise, end-expiratory chest wall volume only slightly decreases, so expansion of tidal volume takes place primarily by encroachment on the inspiratory reserve volume (288). Hence end-inspiratory lung volume reaches close to TLC with consequent increasing of the elastic work associated

with breathing near to TLC [47]. In the presence of significant restrictive mechanical constraints on tidal volume expansion, an increase in ventilatory demand with progressively increased exercise intensities intensifies dyspnea sensations to a greater degree in older compared to healthy young individuals [41, 42].

1.4. Factors impairing exercise tolerance in chronic lung diseases

Ventilatory, gas exchange, cardiovascular and peripheral muscle abnormalities limit exercise tolerance in patients with chronic lung diseases.

1.4.1. Ventilatory constraints

During incremental exercise, healthy elderly individuals increase minute ventilation by 10-15 fold; this is essential to clear the carbon dioxide production and suffice the increased oxygen demand [41-43, 48]. In these circumstances, ventilatory function does not constitute a limiting factor, at least during sub-maximal exercise, as minute ventilation ($\dot{V}_E$) is maintained well below the maximum ventilatory capacity (MVC) [49]. Ventilatory limitation, however, occurs in healthy elderly individuals, particularly women [50] during maximal exercise, as the ratio of $\dot{V}_E$ to MVC ($\dot{V}_E$/MVC) reaches or even exceeds 85% [33, 51].

In the majority of respiratory disorders the $\dot{V}_E$/MVC ratio often exceeds 85% even during submaximal exercise, commonly indicating reduced ventilatory capacity [48, 52]. In fact, in patients with chronic lung diseases, a disparity is developed between the decreased ventilatory capacity, manifested by concurrently reduced capacity to sufficiently increase minute ventilation during exercise and increased ventilatory requirement. This disparity leads to intense breathlesness that is the pivoting symptom limiting exercise in a substantial fraction of patients with chronic lung diseases [53, 54].

The factors contributing to decreased ventilatory capacity and increased ventilatory requirement/workload are outlined below.

Reduced ventilatory capacity during exercise occurs consequently to abnormal respiratory system mechanics and respiratory muscle dysfunction . The high inspiratory (and expiratory) airway resistance and/or reduced compliance may substantially increase airflow pressure requirements thereby increasing the work of breathing [54-56].

Ventilatory demand is increased during exercise secondary to gas exchange abnormalities **(**i.e.: worsening of $\dot{V}_A/Q$ mismatch and increased dead space ventilation) leading to hypoxemia and/or hypercapnia [51]. Ventilatory requirement during exercise is modulated by the metabolic rate, the arterial carbon dioxide tension and the physiological dead space [7]. Metabolic acidosis also increases the ventilatory requirement of exercise [57]. Therefore,, for a given rate of CO_2 output ($\dot{V}CO_2$) and $PaCO_2$, $\dot{V}_E$ is usually increased because of higher dead space ventilation [1] .

1.4.2. Gas exchange limitations

Despite the deterioration in ventilatory reserve with aging, healthy older adults appear able to maintain alveolar ventilation at a level that allows maintenance of arterial blood gases within normal limits, even during heavy exercise [49, 51, 58, 59]. Accordingly, the ventilation-perfusion ratio ($\dot{V}_A/Q$) remains near unity as both ventilation and perfusion increase several-fold with increasing exercise intensity. Moreover, alveolar-capillary diffusion also remains intact, and consequently PaO_2 remains normal, even during high-intensity exercise [48, 49, 51]. Furthermore, in healthy elderly individuals, the increase in tidal volume (V_T) occurs in the setting of a relatively fixed anatomic dead space (V_D), so that the V_D/V_T ratio decreases thereby

promoting an increase in effective alveolar ventilation as a fraction of the increased minute ventilation.

In contrast, in patients with lung diseases gas exchange regulation is impaired during exercise. The impairment involves the airways, the pulmonary vasculature, and the alveolar-capillary interface, thus producing varying degrees of abnormal $\dot{V}_A/Q$ inequalities, diffusion impairment, and hypoxemia [13, 28, 54, 60]. In fact, many patients with severe lung disease experience exercise-induced arterial oxygen de-saturation. Furthermore, arterial PCO_2 may be higher than in healthy subjects as V_D is increased owing to reduced $\dot{V}_A$ [61-63] .

1.4.3. Central and peripheral hemodynamic factors

Cardiac output in healthy elderly subjects increases several-fold in response to exercise [29, 30, 49, 51, 58]. In the majority of healthy elderly subjects, cardiac output is often the "rate-limiting step" to exercise, and at the limit of tolerance, heart rate reaches the maximal predicted. In contrast in chronic lung diseases the physiological mechanisms involved in oxygen transport are frequently impaired resulting in reduction of cardiovascular function secondary to the following reasons. Firstly, coexisting right- or left-ventricular dysfunction may impair exercise function simply because of poor cardiac-output capability, which often compromise oxygen delivery and early development of metabolic acidosis. Similarly, functionally important arrhythmias may also impair the normal increase in cardiac output as a function of an increase in work rate [49, 51, 58, 64]. Secondly, in chronic lung diseases, especially in the presence of pulmonary vascular abnormalities, pulmonary hypertension and right-ventricular dysfunction may develop [65]. These phenomena may worsen in the presence of exercise-induced hypoxemia, which in turn elevate pulmonary vascular resistance and

cause pulmonary arterial hypertension with consequent right-heart failure [60, 65-71]. The resulting restrained increase in cardiac output during exercise, coupled with hypoxemia, reduces systemic oxygen delivery to the locomotor skeletal muscles. Interestingly, there are suggestions that as the work of breathing is often substantially increased in chronic lung diseases during exercise, there might exist a respiratory muscle "steal" of blood flow away from the locomotor muscles, which further compromises peripheral muscle oxygen availability [44, 72].

1.4.4. Skeletal muscle abnormalities

Chronic Respiratory diseases lead to progressively reduced levels of daily activity, chronic under-loading of the locomotor muscles and weakness, which is associated with reduced muscle mass and altered muscle fibre distribution especially with reference to the proportion of type-I (slow-twitch oxidative) fibres [73-79]. Reduction in the proportion of the oxidative fibres compromises the oxidative potential of the muscles and makes these muscles more prone to fatigue during high-intensity exercise. Furthermore, capillary density is also diminished which further reduces regional muscle blood flow and oxygen delivery. Such structural and metabolic abnormalities of the limb muscles may lead to premature metabolic acidosis acidosis and task failure with exercise [73-77].

2.0 Cardiopulmonary Exercise Testing (CPET)

Cardiopulmonary exercise testing is often applied in clinical practice to investigate the mechanisms responsible for the limitation of exercise capacity, and the extent of their contribution (Table 1). This test allows the concurrent study of the function of three organ systems: cardiovascular, respiratory and metabolic of muscle cells in well-

controlled laboratory conditions during exercise [80]. At the same time, cardiopulmonary exercise testing (CPET), allows recordings of subjective factors such as dyspnea and muscle discomfort in conditions where symptoms are apparent or become more pronounced. CPET test indicated in patients with limited exercise capacity, when the causes of exercise limitation have not been sufficiently clarified following a thorough respiratory or central hemodynamic evaluation [81, 82]. Applications of CPET are presented in table 2.

The most widely used types of exercise testing that are applied in the clinical evaluation of patients are the incremental exercise test to the limit of tolerance and the constant-load exercise test sustained at a fraction of peak exercise capacity. More often these tests are conducted on an electromagnetically braked cycle ergometer [84].

Table 1. Mechanisms limiting exercise capacity in chronic respiratory diseases.

1) Expiratory flow limitation
2) Exercise-induced dynamic hyperinflation
3) Increased work of breathing
4) Disturbance between alveolar ventilation / perfusion ratio
5) Impaired cardiac performance
6) Peripheral muscle dysfunction

Table 2. Diagnostic uses of exercise testing

1) Myocardial ischemia
2) Peripheral vascular disease
3) Exercise-induced asthma
4) Unfitness
5) Psychogenic dyspnea
6) Muscle phosphorylase deficiency

2.1 Types of cardiopulmonary exercise testing

2.1.1 Incremental exercise

This test subjects the patient to a gradually increase of load upon all physiological systems responding during exercise. The intensity gradually increases until symptoms of dyspnea and / or muscle discomfort limit further increase of the imposed work. This test allows determination of biological responses of transport and utilization of oxygen up to the limit of exercise tolerance (i.e. the peak oxygen uptake (VO_2peak). Furthermore when the test is performed on a cycle ergometer, the rate of change of oxygen uptake (VO_2) in relation to the work rate (WR) reflects the sufficiency of the operating physiological systems involved in the transport to and utilization of oxygen by the operating organs during conditions of increasing external load [80, 82, 83] (Figure 1).

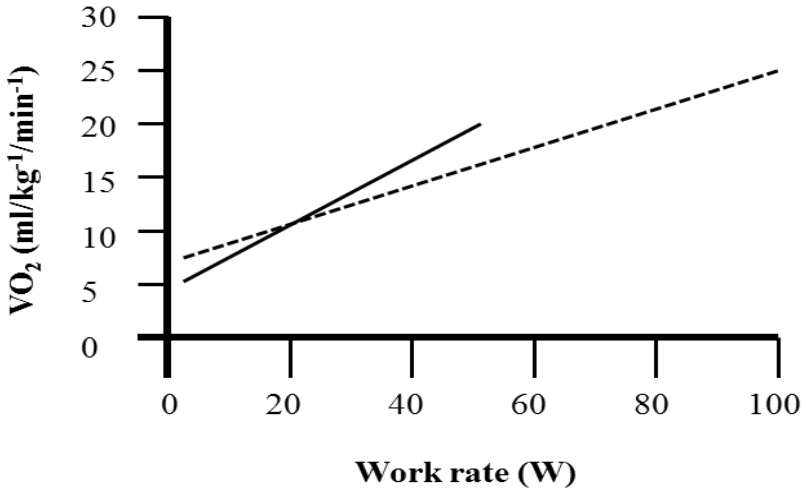

Figure 1. *Change of the oxygen uptake in relation to work rate on a cycle ergometer in a healthy individual (dotted line) and in a patient with COPD (solid line).*

2.1.2 Constant-load exercise

During constant-load exercise testing, the patient is asked to perform work that corresponds to a certain fraction of his/her peak exercise capacity (which typically ranges between 50 to 75%) to the limit of tolerance caused by intense dyspnea and/or muscle discomfort symptoms (Figure 2). The period of dynamic adaptation until

stabilization of cardiorespiratory and metabolic responses provide valuable information about the operation and response of the capacity of the respiratory, cardiovascular and metabolic systems to sufficiently respond to a given load [85, 84]. Table 3 shows the effect of different types of interventions during constant load exercise in patients with COPD [83].

Table 3. Effect of different types of interventions during constant-load exercise in patients with COPD.

Type of intervention	Medication (Tiotropium)	Oxygen supplementation 50%	Helium (79%) and oxygen (21%) supplementation	Rehabilitation
Exercise intensity, (%) predicted	75	75	80	75
Change in exercise tolerance time (%)	+21	+145	+115	+224
Change in inspiratory capacity (%)	+12	+24	+12	+15
Change in dyspnea sensation (%)	-14	-40	-25	-30

Besides the two aforementioned tests, there are tests that provide less information concerning the physiological responses, but even like this they allow the determination of the exercise capacity to some extent. The most widely used test is the 6 minute walk test, which is submaximal and is often applied to evaluate the efficacy of pharmaceutical or non-pharmaceutical interventions [83].

2.2 Recorded variables during cardiopulmonary exercise testing

Peak oxygen uptake (VO_2peak): The classic criterion for the determination of exercise capacity and cardiorespiratory efficiency is provided by recording peak oxygen uptake. In a well-executed incremental test, the peak oxygen uptake reflects the

maximum aerobic capacity. This parameter reflects the oxygen binding capacity of hemoglobin molecules in alveolar level, the transfer to the periphery through the mediation of the cardiovascular system and its utilization by mitochondria in skeletal muscle to produce external work. Values lower than 80% predicted are considered abnormal and values below 50% predicted indicate serious dysfunction of the above physiological systems (Table 4) [82, 83].

Anaerobic threshold: The anaerobic threshold (AT) is often considered as an index for the initiation of metabolic acidosis, which is the result of the increase of lactic acid in arterial blood during exercise [85]. Normal values when detecting the anaerobic threshold represent at least 45% to 50% of peak oxygen uptake (Table 4).

Table 4. Values of physiological responses in a patient with COPD during incremental exercise testing, expressed as a fraction of the expected values in healthy individuals.

Variable	Predicted	Measured	Presentence of predicted (%)
Peak oxygen uptake, VO_2 peak (liters / minute)	1.67	0.90	54
Peak heart rate (beats / minute)	151	136	90
Peak work rate (Watt)	60	30	50
Peak oxygen pulse (ml / beats)	11.1	6.6	60
Change in oxygen uptake / Change in work rate $\Delta VO_2/\Delta WR$ (ml / minute / watt)	10.3	8.9	-
Anaerobic threshold (liters / minute of VO_2)	1.0	0.5	50
Peak ventilation V_E (liters / minute)	90	40	45

Oxygen pulse: It reflects the amount of oxygen extracted from the peripheral muscles within each heartbeat. According to the modified equation of Fick, the oxygenic pulse is numerically equal to the product of stroke volume (SV) and arteriovenous oxygen difference ($C(a\text{-}v)O_2$), i.e. $VO_2/HR = SV * C(a\text{-}v)O_2$ and is commonly used as an index of stroke volume during exercise [83].

Breathing reserve: The degree of ventilatory limitation profoundly contributes to the impaired exercise capacity, and can be evaluated from the respiratory reserve, which reflects the relationship of respiratory requirement in relation to respiratory capacity. For most healthy adults, the maximum pulmonary ventilation (V_E) during exercise does not exceed 70% of maximum voluntary ventilation (MVV), although this fraction may increase ($V_E/MVV > 0.75$) indicating limited respiratory reserve in chronic cardiorespiratory diseases [80, 82, 83].

2.3 Pathophysiological manifestations

2.3.1 Chronic Obstructive Pulmonary Disease (COPD)

Reduced exercise capacity in patients with COPD is usually manifested by reduced peak oxygen uptake (Figure 3A), and early onset of the anaerobic threshold, which reflects early metabolic acidosis. The premature termination of exercise testing is accompanied by additional low value of peak pulmonary ventilation (V_E) (Figure 3B), and by breathlessness (Figure 3C) and muscle discomfort [80].

It is well documented that exercise tolerance during constant-load testing on a cycle ergometer largely depends on the imposing load, as the time to the limit of tolerance in patients with COPD decreases proportionally to increasing power output. Studies have shown that the rate of change in oxygen uptake during the transitional phase from unloading cycling to constant-load exercise is faster in healthy individuals

(approximately 35 sec) compared to patients with COPD (approximately 75sec) [85] (Figure 2). The slower kinetic response of oxygen uptake is considered to lead to an early and greater reliance on anaerobic metabolism causing the accumulation of by-products of metabolism accelerating the onset of muscle fatigue [85].

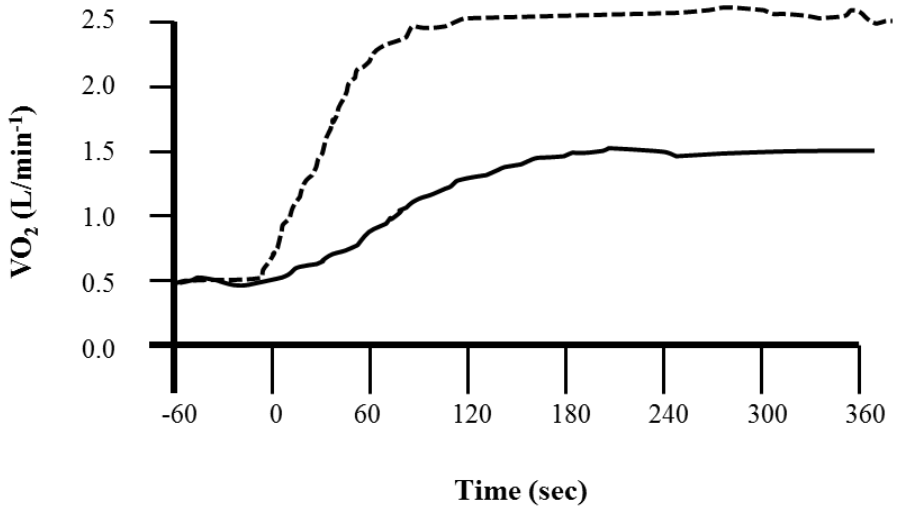

Figure 2. Changes in oxygen uptake during the transition from unloading exercise to constant-load exercise in a healthy man (dotted line) and in a patient with COPD (solid line).

2.3.2 Interstitial Lung Disease

During cardiopulmonary exercise testing, the peak values of work rate and oxygen uptake (Figure 3A), the oxygen tension in the arterial blood (Figure 3D), and the respiratory reserve are all reduced in patients with interstitial lung disease, compared to healthy individuals. For given oxygen consumption the rate of increase of pulmonary ventilation (V_E) is disproportionately increased compared to healthy age-matched individuals (Figure 3B). At peak exercise tolerance a significant heart rate reserve is observed as peak heart rate is reduced.

During constant-load exercise, patients with interstitial lung disease have increased pulmonary ventilation (V_E), for a given load or a given oxygen consumption, and increased values of the produced carbon dioxide output (VCO_2) due to increased dead

space ventilation. In these patients, the ratio between minute ventilation to oxygen uptake (VO_2) and the produced carbon dioxide (VCO_2) is abnormally high. The occurrence of arterial hypoxemia during cardiopulmonary exercise testing is commonly associated with an unusually broad arteriovenous oxygen difference and reduced tissue oxygenation. These factors play an important role in the early onset of metabolic acidosis during submaximal exercise. Thus, limitation of exercise tolerance is often due to symptoms of both dyspnea and discomfort of the lower limbs [80, 82, 83].

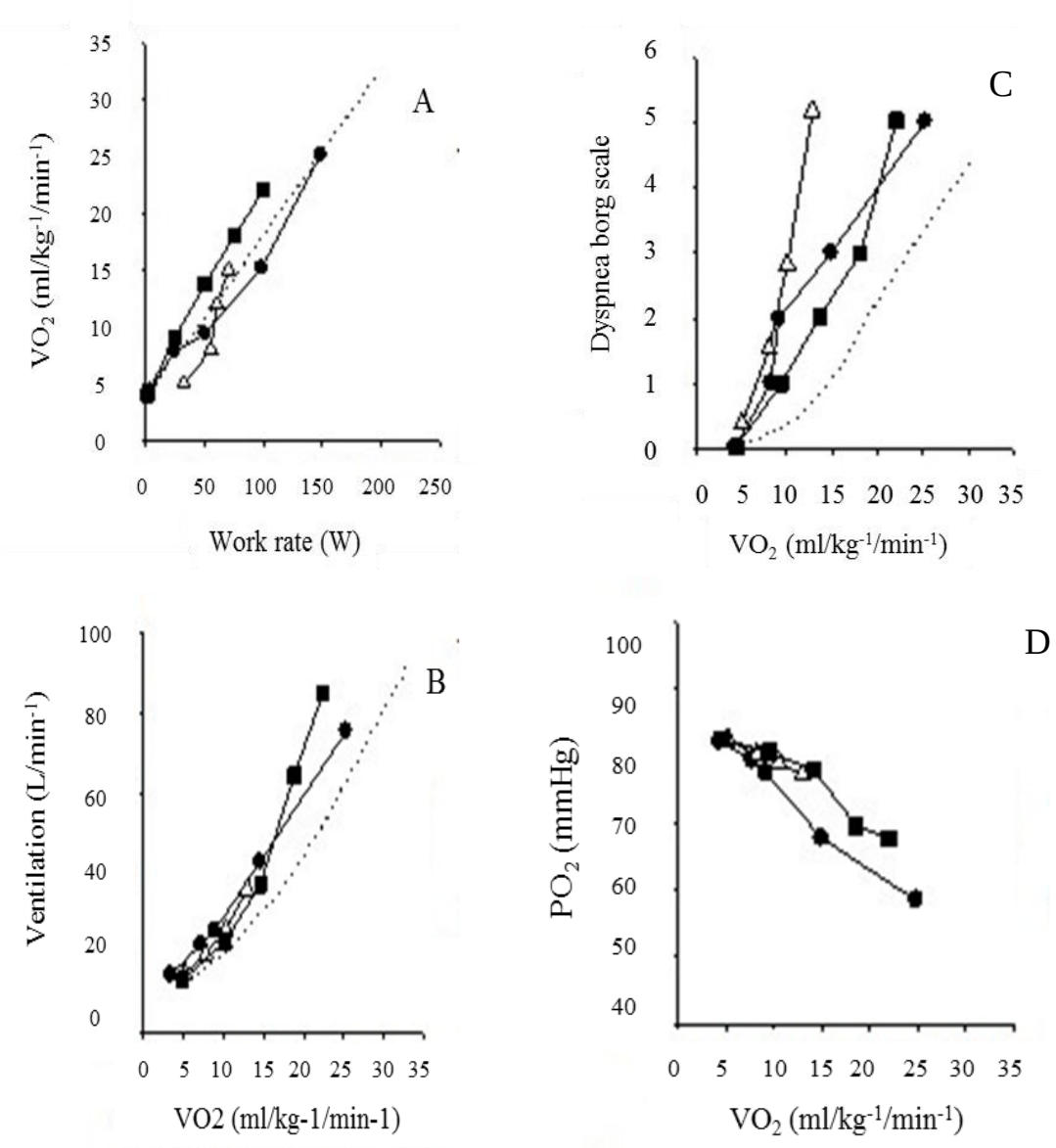

Figure 3. Responses of A: oxygen uptake, B: pulmonary ventilation, C: dyspnea sensations and D: oxygen tension in the arterial blood during cardiopulmonary exercise testing in patients with COPD (triangles) with pulmonary hypertension (squares), with

interstitial lung diseases (circles) compared with healthy age-matched individuals (dotted lines). [80]

2.3.3 Pulmonary Hypertension

During cardiopulmonary exercise testing, peak values of oxygen uptake (VO_2) (Figure 3A) and of work rate are reduced in patients with pulmonary hypertension compared to healthy age-matched. However, the slope of the relationship of the oxygen uptake over the work rate is normal (Figure 3A). At peak exercise tolerance heart rate reaches the maximum predicted value, whilst pulmonary ventilation exceeds 85% of maximum voluntary ventilation (Figure 3B), thus exercise in these patients is often limited by both cardiovascular and respiratory factors [80, 83].

During submaximal exercise these patients exhibit tachycardia due to increased pulmonary vascular resistance and the consequent increase in the afterload of the right ventricle, which limits the increase in stroke volume. On the other hand, excessive enlargement of arteriovenous oxygen tension and an unusually high ratio between pulmonary ventilation and carbon dioxide output, implies an increase of dead space ventilation due to the high heterogeneity between alveolar ventilation and blood flow (VA/Q) causing severe hypoxemia (Figure 3D). Such a model of cardiopulmonary disorder promotes early onset of metabolic acidosis, limits the quantity of readily available oxygen to peripheral muscles, thereby causing premature occurrence of peripheral muscle fatigue [80, 82, 83].

3.0 CPET: a tool for predicting mortality

Cardiopulmonary exercise testing emerges as a useful tool for the prognosis of mortality in patients with lung diseases. Peak oxygen intake is the most important predictor of mortality rate at a depth of 5 years in patients with Chronic Obstructive Pulmonary Disease and is a significant predictor of survival in patients with pulmonary

hypertension [82, 83]. In patients with interstitial lung disease, cardiopulmonary exercise testing has proved particularly useful in predicting the prognosis of the disease. The peak oxygen consumption, oxygen consumption corresponding to the anaerobic threshold, and the slope of change in pulmonary ventilation over carbon dioxide output are useful predictors of patient survival with chronic respiratory diseases, however, a wider range of factors are also playing an important role in the survival of these patients and thus they should be taken into account [81, 83, 84].

4.0 CPET: a tool for evaluating exertional dyspnoea

Why is cardiopulmonary exercise testing (CPET) an important tool for exploring exertional dyspnoea ("dyspnoea which occurs during exercise") both in research and clinical settings? For several reasons: 1) CPET may help researchers and clinicians explore and unmask the physiological mechanisms (interaction between them) underlying this symptom in a broad spectrum of cardio-respiratory disorders; 2) CPET may also help clinicians identify additional mechanisms underpinning the greater dyspnoea intensity which could stand as "independent of" or "not directly related to" the main/obvious pathophysiological determinant of the disease under consideration; CPET may also be utilised to explore the mechanisms by which exertional dyspnoea can be altered (ameliorated) after pharmacological and non-pharmacological interventions.

Why is exertional dyspnoea worth documenting and accurately assessing? For at least the following reasons: 1) activity-related dyspnoea is usually the earliest and most troublesome complaint for which patients with cardio-pulmonary diseases seek medical attention; 2) this symptom progresses relentlessly as the underlying disease advances leading invariably to avoidance of activity with consequent skeletal muscle

deconditioning and an impoverished quality of life; 3) up to a quarter of the general population and half of severely ill patients are affected by this symptom; 4) dyspnoea is also an important predictor of quality of life, exercise tolerance and mortality in various conditions. In patients with chronic obstructive pulmonary disease (COPD), dyspnoea has been found to be a better predictor of mortality than forced expiratory volume in 1 s (FEV1). In patients with heart disease referred for clinical exercise testing, it is a better predictor of mortality than angina; 5) dyspnoea is also associated with decreased functional status and worse psychological health in older individuals living at home; 6) it is also a factor in the low adherence to exercise training programmes in sedentary adults and in patients with COPD; 7) the effective management of exertional dyspnoea remains a major challenge for caregivers, and modern treatment strategies that are based on attempts to reverse the underlying chronic condition are only partially successful [85-91].

Two recent review articles [85, 92] have explored and clarified in greater details the physiological mechanisms underlying exertional dyspnoea and their applications in reaserach and clinical practice.

Dyspnoea is a complex, multifaceted, highly personalised and multidimensional symptom comprising three major dimensions (the sensory-perceptual domain, the affective distress, and the symptom impact or burden), the perception of which involves the integration of afferent and efferent inputs at cortical level and is modulated by affective/emotional/behavioural components, as recently stated by the American Thoracic Society [93] and European Respiratory Society [85].

There is no unique central or peripheral source of this symptom. The definition given by the latest ATS statement (*a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity*) highlights the

importance of the different qualities (descriptors) covered by the term dyspnoea, the cortical integration of multiple sources of neural inputs about breathing and the physiological affective and behavioral consequences [93]. Dyspnoea is believed to arise when there is a conscious awareness of dissociation between what the brain expects (through the "corollary discharge", i.e., copy of the descending motor activity to perceptual areas) and what it receives in terms of neural inputs from the respiratory system, respiratory muscles, peripheral chemoreceptors and locomotor muscles [93]. It goes without saying that not all conscious breathing sensations can be labelled as "dyspnoea" because the brain is able to "filter" all the respiratory sensations and let only some of them reach the conscious level [85]. This sensory gating process hinders the brain from being constantly overloaded by irrelevant sensory information. Human beings have the voluntary capacity to bring "breathing" into awareness at any moment. On the other hand, breathing may come to conscious awareness automatically if it needs to be attended to (gate-in). This "gating process" is instrumental in monitoring essential biological and physiological functions and adopting appropriate behaviour. It has been proposed that respiratory sensations are the result of neural gating into the cerebral cortex of respiratory afferent input eliciting a somatosensory cognitive awareness of breathing and an affective response [85].

For a pedagogic purpose we can summarise in a very simplistic way that dyspnoea may stem from two processes: 1) a discriminative one which identifies relevant afferent information on respiratory disruption/abnormalities and brings them to consciousness (sensory components: intensity and quality); and 2) an affective one which labels the now conscious sensation as unpleasant or threatening, i.e. dyspnoea.

Dyspnoea is not a single sensation, and our brain is able to distinguish among different afferent information and give each of them a distinct cognitive sensation, notably: 1)

work/effort (‘‘breathing requires work or effort’’); 2) *tightness* (‘‘chest is constricted, chest feels tight’’); and 3) *air hunger* (‘‘unsatisfied inspiration, starved for air, urge to breathe, like breath holding’’). It is generally accepted that these sensations do not share the same physiological mechanisms [85, 93]. Some of these sensations, such as *work/effort* and *air hunger* may exist and vary independently in the same subject or experimental condition. Notwithstanding, whether there are multiple types of dyspnoea, whether they are subjective expression of different neurophysiological mechanisms or the same neurophysiological mechanisms may be expressed differently in relation to language, psychological, cultural, and/or social context) is at the moment unclear and required additional research.

Can dyspnoea also be quantified (“intensity”). Yes, exertional dyspnoea can be easily defined as "the perception of respiratory discomfort that occurs for an activity level that does not normally lead to breathing discomfort". It follows that the intensity of dyspnoea can be determined by assessing the activity level required to produce dyspnoea (i.e. dyspnoea at rest is more severe than dyspnoea when climbing stairs) [85]. Dyspnoea can therefore be assessed during a physical task, such as CPET [85, 93]. For this purpose, the 10-point Borg scale can be used to rate a specific respiratory sensation (e.g., inspiratory difficulty, breathing effort, expiratory difficulty, air hunger, etc.) or a more general one (e.g., breathing difficulty, breathlessness). The magnitude of respiratory sensation is anchored at both extremes of the scale such that a rating of “0” represents no breathing discomfort and “10” represents the maximal breathlessness that the subject had ever experienced or could imagine experiencing. The visual analogue scale (VAS) is another dyspnoea measuring instrument with proven construct validity used during CPET. Both the VAS and Borg scale have been shown to provide similar scores during CPET, and to be reliable and reproducible over time in healthy

subjects, and in patients with chronic respiratory diseases undergoing CPET [84]. The advantage of using the Borg or VAS scales in individual patients is the possibility of reliably comparing "intensity of exertional dyspnoea" at the same level of exercise activity (*standardised* work-rate or oxygen consumption or ventilation during CPET) between subjects, and before and after a pharmacological and/or non-pharmacological treatment [84]. Studies in cardiopulmonary diseases have shown that during CPET there is a close correlation between the magnitude (and duration) of respiratory effort (measured by tidal oesophageal pressure relative to maximum) and the intensity of dyspnoea (measured by the Borg scale), and that pharmacological manipulations able to reduce the magnitude (and duration) of respiratory effort are clearly and consistently associated with reduced dyspnoea intensity [84, 85].

The interest of using CPET in this setting is also that quality and quantity of dyspnoea can be measured together during CPET. Few studies have shown that moderate-to-severe chronic obstructive pulmonary disease (COPD) and even mild stable asthmatics are able to "perceive" dynamic changes in their mechanics of breathing during exercise: once a critical inspiratory reserve volume (IRV) is attained (0.3-0.5L from total lung capacity), tidal volume expansion is critically constrained, dyspnoea intensity rises abruptly and there is a transition in the dominant qualitative descriptor choice from *work/effort* to *difficult/unsatisfied inspiration* [85]. The clinical relevance of these findings is that by asking the quality of dyspnoea at the end of an exercise bout one can ascertain whether a critical IRV (*difficult/unsatisfied inspiration*) or not (*work/effort*) has been reached, i.e., the likelihood of developing exercise-related critical volume constraints [85]. Exertional dyspnoea is by far the dominant symptom in patients with Pulmonary Arterial Hypertension (PAH) [94-96]. Recent advances in PAH have highlighted the importance of respiratory mechanical anomalies easily detectable

during CPET in contributing to exertional dyspnoea in PAH patients; some of them (up to 60%) may exhibit reduced expiratory flows in tidal operating range, which could promote exercise-induced dynamic lung hyperinflation, and this can be a major source of dyspnoea on exertion also in this population [94]. Although exertional dyspnoea in these patients is likely multifactorial, the increased ventilatory demand and abnormal dynamic ventilatory mechanics need be considered in PAH patients [94], in the absence of respiratory muscle dysfunction [96] or TLC changes [94].

CPET can also be used to evaluate mechanisms of exertional dyspnoea in chronic heart failure. Heart failure patients may report dyspnoea alone or in variable combination with leg discomfort as the exercise limiting symptoms. In heart failure no hemodynamic and respiratory variables, either at rest or during exercise, seem to be able to discriminate between heart failure patients who complain of dyspnoea as the predominant exercise limiting symptom from those who report leg discomfort. Clearly the issue is still unsolved and more studies are needed [85].

We hope we have convinced the reader of the crucial importance of using CPET for the global evaluation of exercise tolerance as well as for evaluating the physiological mechanisms underlying the perception of exertional dyspnoea that can be amenable to therapeutic interventions.

5.0 Conclusions

Functional measurements at rest do not always provide an accurate diagnosis and a proper stratification of severity in patients with chronic respiratory diseases. Cardiopulmonary exercise testing complimentary applied to functional tests at rest, provides useful information on exercise capacity and a comprehensive evaluation of the

biological and phisiological mechanisms that limit exercise tolerance and underpin exertional dyspnoea in all cardiorespiratory disorders.

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